Michael K. Johnson
JOHNSON BECKER, PLLC
33 South 6th Street, Suite 4530
Minneapolis, MN 55402
Telephone: (612) 436-1800
Facsimile: (612) 436-1801
mjohnson@johnsonbecker.com

Ryan L. Thompson
WATTS GUERRA LLP
5250 Prue Road, Suite 525
San Antonio, Texas 78240
Telephone: (210) 448-0500
Facsimile: (210) 448-0501
rthompson@wattsguerra.com

Max Kennerly
THE BEASLEY FIRM
1125 Walnut Street
Philadelphia, PA 19107
Telephone: (215) 931-2634
Facsimile: (215) 592-8360
max.kennerly@beasleyfirm.com

Hunter J. Shkolnik
NAPOLI, BERN, RIPKA & SHKOLNIK LLP
350 Fifth Avenue
New York, New York 10018
Telephone: (212) 267-3700
Facsimile: (212) 587-0031
hunter@napolibern.com

Tor A. Hoerman
TORHOERMAN LAW LLC
101 W. Vandalia Street, Suite 350
Edwardsville, Illinois 62025
Telephone: (618) 656-4400
Facsimile: (618) 656-4401
thoerman@torhoermanlaw.com

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

Relates to: ALL CASES

Master File No.: 3:13-md-02452-AJB-MDD

MDL – 2452

PLAINTIFFS' MEMORANDUM OF POINTS AND AUTHORITIES IN OPPOSITION TO DEFENDANTS' MOTION FOR SUMMARY JUDGMENT BASED ON PREEMPTION

Date: July 1, 2014
Time: 9:30 a.m.
Courtroom: 3B
Judge: Hon. Anthony J. Battaglia
Magistrate: Hon. Mitchell D. Dembin

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Preemption is a fact-intensive affirmative defense on which Defendants bear the burden of proof. They have not made even a *prima facie* showing of impossibility, much less shown facts establishing its elements "beyond peradventure" as required. The motion is also absurdly premature because Plaintiffs have not been allowed meaningful discovery on preemption issues, and thus, under Fed. R. Civ. P. 56(d), cannot present the "facts essential to justify [their] opposition" to the motion. If this motion is not denied outright, it should be continued or taken off the calendar until Plaintiffs have had the opportunity to take the discovery necessary to fully address the motion.

INTRODUCTION

A defendant moving for summary judgment on an affirmative defense "must establish beyond peradventure all of the essential elements" of the defense. *Trigueros*, *infra*. As a practical matter, impossibility preemption requires that the defendant propose or unilaterally implement the type of warning suggested by the plaintiff, and the FDA must then prohibit that warning "because the agency deemed such a warning inappropriate." *Levine*, *infra*. The defendant must also prove that it fully disclosed to the FDA all information that could have affected the FDA's analysis. *Glynn*, *infra*.

Only two federal courts have found "impossibility" preemption in a branded prescription drug product liability case. In *Dobbs*, *infra*, the Court found after full discovery that the FDA thrice rejected the manufacturer's attempts to add a warning like the warning sought by the plaintiff. The FDA also articulated a concrete reason why it believed the warning would do more harm than good. In *Glynn*, *infra*, the FDA rejected the very warning proposed by the plaintiff, but the court still allowed complete discovery *and* held a trial to confirm that the manufacturer had not withheld information from the FDA, and that the manufacturer could not have successfully used the CBE process to modify the label.[1] Otherwise, federal courts have unanimously denied preemption to

[1] *Glynn* found impossibility, but it is no mystery why Defendants omitted reference to the case: *Glynn* reaffirmed that a defendant cannot meet its burden of proof on preemption without full discovery establishing that it performed adequate trials, studies and

manufacturers of branded prescription drugs, even where the manufacturer could point to years of intense FDA scrutiny, independent FDA studies, and an unwavering FDA stance against Citizen's Petitions for strengthened warnings (*see*, *e.g.*, *Mason*, *infra*).

Legally, Defendants' motion is predicated on the erroneous assertion that they cannot add warnings to their product labels without FDA approval.[2] The Supreme Court rejected that very claim in *Levine*. Factually, Defendants' entire motion is based on an extraordinary manipulation of a journal article published by FDA staff. Here is the conclusion of that article, with the parts *omitted* by the Defendants (Defs' Br., pp. 1–2) put back in and **bolded:**

> [A]ssertions concerning a causal association between incretin-based drugs and **pancreatitis or** pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. **The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed[3] provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. The FDA and the EMA believe that** the current knowledge is adequately reflected in the product information or labeling, **and further harmonization among products is planned in Europe.**

Defendants' strident assertion that the FDA "specifically rejected" a link between their drugs and pancreatic cancer is pure fiction (Defs' Br., p. 1). The FDA *actually* said it has "not reached a final conclusion at this time regarding such a causal relationship." Defendants' claim that the FDA has concluded "the current knowledge is adequately

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pharmacovigilance, and fully disclosed all relevant data to the FDA — exactly what the incretin Defendants have sought to avoid since day one.

[2] Defs' Br., p. 4: "[the] FDA must approve any labeling changes that become necessary in light of post-approval studies or experience;" *compare Levine* at 1199: "The CBE regulation permitted Wyeth to *unilaterally* strengthen its warning…." (emphasis added).

[3] The FDA has not disclosed the data it reviewed. Given Defendants' burden to prove the FDA's hypothetical "intent" in response to a hypothetical warning and the data supporting that warning, this motion cannot be granted until discovery has revealed the full scope of what data the Defendants "would have" provided with that warning, *i.e.*, all data that could show a causal association.

reflected in the product information or labeling" (Defs' Br., pp. 1, 2, 3, 9, 11, 18, 20) fares little better: the "labeling" language plainly refers to *pancreatitis*, a harm warned about by *all* of the drugs in this MDL, hence the reference to "harmonization" of the warnings.

There is no indication that Defendants will ever be able to meet their burden of proof. They offered no evidence of having proposed or unilaterally implemented any warning like the warning proposed by Plaintiffs,[4] followed by clear factual evidence showing that the FDA intended to reject that warning. Instead, Defendants ask this Court to speculate about what the FDA *might* do in response to a hypothetical pancreatic cancer warning. The Supreme Court has taken a dim view of regulatory speculation to meet a burden of proof, *Mensing*, *infra*, and such speculation would be particularly inappropriate here given the lack of discovery on what the FDA knew and when, and what the Defendants have withheld from the FDA.[5]

Finally, Defendants moved for summary judgment on their own affirmative defense prior to responding even to Plaintiffs' general causation discovery, and with *no* discovery pending on regulatory issues. If not denied, the motion should be continued until Plaintiffs have taken discovery necessary to their opposition. Fed. R. Civ. P. 56(d).

I. THE LEGAL STANDARDS FOR IMPOSSIBILITY PREEMPTION

A. Standard Of Review: Beyond Any Doubt On Any Element

Defendants wrongly assert that, once they have made an "initial" argument for impossibility preemption, the burden shifts to Plaintiffs to show state tort claims are *not* preempted. Defs' Br., p. 10 n. 29. In fact, because they bear the burden of proof,[6] they

[4] Plaintiffs have not submitted a proposed label in this case, nor could they before completing discovery into general causation, regulatory matters, labeling changes, marketing, and prescribing physicians.

[5] Much as an injured plaintiff cannot prove what he or she "would have" earned in wages by only presenting the *good* parts of their employment history, Defendants cannot prove what the FDA "would have" done with a hypothetical proposed warning by only presenting the evidence that *helps* them.

[6] *See, e.g.*, *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 255 (1984).

"must establish beyond peradventure[7] *all* of the essential elements of the claim or defense to warrant judgment in [their] favor." *Trigueros v. Southwest Airlines*, 2007 U.S. Dist. LEXIS 64234 at *5 (S.D. Cal. Aug. 29, 2007)(emphasis in original, *quoting Fontenot v. Upjohn Co.*, 780 F.2d 1190, 1194 (5th Cir. 1986)); *accord Ash v. Bank of Am. N.A.*, 2014 U.S. Dist. LEXIS 10457 at *34 (E.D. Cal. Jan. 27, 2014). In other words, Defendants "must *affirmatively* prove the lack of *any* issue of material fact as to each element of the claim/defense pled" by way of "admissible evidence," whereas "the opposing party need only produce evidence sufficient to raise a genuine issue of material fact as to any one element in order to defeat the motion." *E. & J. Gallo Winery v. EnCana Energy Servs.*, 2008 U.S. Dist. LEXIS 46927, 25 (E.D. Cal. May 23, 2008)(emphasis in original). This is a "heavier burden" than normally found when the movant on summary judgment does not bear the burden of proof at trial, because the "district court does not 'weigh evidence' and must make every inference in favor of the non-moving party." *Id.* quoting *Suzuki Motor Corp. v. Consumers Union of the U.S., Inc.*, 330 F.3d 1110, 1140 (9th Cir. 2003).

Further, in the context of preemption, "[i]n order to meet its burden, [the manufacturer] must identify the state law duties associated with the remaining causes of action and provide the Court with an analysis of how those duties conflict with federal law." *Gannon v. Bayer (In re Yasmin & Yaz (Drospirenone))*, 2014 U.S. Dist. LEXIS 56862, 33-34 (S.D. Ill. Apr. 23, 2014) (citation omitted, denying preemption).

B. State Tort Law Plays A Role Alongside FDA Regulation

There is a presumption against preemption of state tort claims against drug manufacturers. "So long as Congress has set foot in a 'field which the States have traditionally occupied,' the presumption applies." *McDaniel v. Wells Fargo Invs., LLC*, 717 F.3d 668, 675 (9th Cir. 2013) (quoting *Wyeth v. Levine*, 555 U.S. 555, 575 (2009)). In *Wyeth v. Levine*, the Supreme Court found that Congress had an "awareness of the

[7] The Oxford Dictionary defines "peradventure" as "uncertainty or doubt as to whether something is the case." As the Supreme Court stated in describing the "beyond a peradventure," standard, "It is seldom that such certainty of proof is possible." *Marx v. Ebner*, 180 U.S. 314, 319 (1901).

prevalence of state tort litigation," but repeatedly refused to expressly preempt claims, which was "powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Levine* at 574-75 (citations omitted). The defendant in *Levine* (Wyeth) claimed it could not add or strengthen its drug's warning label without FDA approval, and thus argued that the FDA's approval was "both a floor and a ceiling for drug regulation." *Levine* at 573. The Supreme Court rejected this argument, in part because the "changes being effected" (CBE) regulation allows manufacturers to *unilaterally* "add or strengthen" a "contraindication, warning, precaution, or adverse reaction," and in so doing, they "need not wait for FDA approval." *Id*. at 568. Moreover:

> Wyeth's cramped reading of the CBE regulation and its broad reading of the FDCA's misbranding and unauthorized distribution provisions are premised on a more fundamental misunderstanding. Wyeth suggests that the FDA, rather than the manufacturer, bears primary responsibility for drug labeling. Yet through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that **the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.**

Levine, 555 U.S. at 570-71 (citations omitted; emphasis added); *accord PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2574 (2011) ("A brand-name manufacturer seeking new drug approval is responsible for the accuracy and adequacy of its label."). Given the FDA's reliance on manufacturers' self-reporting of data and branded drug manufacturers' independent duties and powers, tort claims are not preempted.[8]

C. *Levine* Rejected Defendants' Argument That The Misbranding Regulations Create Impossibility Preemption

As Defendants do here, Wyeth argued in *Levine* that, "if it had unilaterally added such a warning, it would have violated federal law governing unauthorized distribution

[8] Experience has borne out the need for tort litigation. *See* Institute of Medicine, "The Future of Drug Safety," 2007, p. 4, *available at*: http://www.nap.edu/openbook.php?record_id=11750&page=4 (FDA and pharmaceutical industry do not communicate "safety concerns in a timely and effective fashion").

and misbranding." 555 U.S. at 570.[9] The Court rejected the argument, but recognized two instances in which a tort claim could potentially be preempted: first, where the manufacturer actually "attempted to give the kind of warning required by the [state] jury but was prohibited from doing so by the FDA," or, second, where the manufacturer attempted to give that warning and can prove, "as a matter of fact," that "the FDA intended to prohibit it from strengthening the warning about [the drug] because the agency deemed such a warning inappropriate." *Id.*

The Court reiterated that "impossibility pre-emption is a demanding defense," expressed skepticism that true impossibility would ever actually occur,[10] recognized that misbranding is a fact issue decided by a jury and not by the FDA,[11] and reiterated the "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." Given that context, "clear evidence that the FDA would not have approved a change" requires, at a minimum, clear[12] *factual* evidence that the manufacturer presented a warning like the warning proposed by Plaintiffs, but the FDA "intended to prohibit" it.

Defendants argue for a complete inversion of *Levine*. They begin with the exact argument rejected by *Levine*,[13] ignore the CBE regulations, present no factual evidence *at all* relating to labeling submissions or rejections, and then assert that continued FDA approval is itself proof the FDA would reject a labeling change. Defendants' proposed

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[9] Apart from the same misbranding and unauthorized distribution regulations interpreted against them in *Levine*, Defendants rely on cherry-picked phrases from two Federal Register publications from the 1970s. Plaintiffs' search revealed no post-*Levine* opinion even discussing those publications.

[10] As the Court said, "the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept…" *Levine*, 555 U.S. at 570.

[11] "[T]he FDA's belief that a drug is misbranded is not conclusive." *Levine*, 555 U.S. at 570.

[12] The Supreme Court often uses "clear evidence" to mean "clear and convincing." *See, e.g.*, *Microsoft Corp. v. i4i Ltd. Partnership*, 131 S. Ct. 2238, 2243 (2011).

[13] "[The] FDA must approve any labeling changes that become necessary in light of post-approval studies or experience." Defs' Br., p. 4.

"ultimate inquiry" revolves around evaluating whether there is "'reasonable evidence of a causal association' with the medication and a 'clinically significant hazard,'" Defs' Br., p. 15 (quoting FDA misbranding regulations).

Defendants' approach is fatally flawed. Initially, they have not "addressed the Supreme Court's finding that manufacturers are presumptively able to make label changes … without FDA approval under the CBE process," and thus Defendants "[have] provided no evidence, let alone clear evidence…." *Dopson-Troutt v. Novartis Pharms. Corp.*, 2013 U.S. Dist. LEXIS 135834, *22 (M.D. Fla. Sept. 23, 2013) (rejecting impossibility preemption).[14] Their motion should be denied on that basis alone.

Moreover, Defendants' "ultimate inquiry" is "nothing more than creative paraphrasing of the FDA's regulations." *Gaeta*, *infra*. Defendants are attempting to revive the argument rejected by *Levine*, *i.e.*, that federal regulations are "a floor and a ceiling for drug regulation," and so a plaintiff can only overcome preemption if they prove Defendants' drugs are misbranded by not carrying a warning. As *Levine* recognized, the FDA's belief that a drug's label is compliant with the regulations is axiomatic and necessarily true of all drugs on the market, but "the mere fact that the FDA approved Phenergan's label does not establish that it would have prohibited such a change." Unsurprisingly, other MDLs have rejected similar attempts to re-write *Levine*.[15]

D. Post-*Levine* Precedent Shows The Essential Element of Impossibility Is An Actual FDA Rejection For Safety Reasons

Preemption is indeed a "demanding" defense, and thus branded prescription drug manufacturers have been met with universal rejection by the circuit courts.[16] Courts in

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[14] *Accord Hill v. Novartis Pharms. Corp.*, 944 F. Supp. 2d 943, 956 (E.D. Cal. 2013) (Defendants "ignore[d] the discretion given to the manufacturer…").

[15] "[T]he defendants appear to misunderstand their federal labeling-law duties as they might relate to preemption. The *Levine* court emphasized that … it remains the duty of the drug's manufacturer to appropriately warn about the potential dangers of the drug." *In re Actos (Pioglitazone) Prods. Liab. Litig.*, 2014 U.S. Dist. LEXIS 1749, *32-33, (W.D. La. Jan. 7, 2014) (denying preemption).

[16] *See, e.g., Wimbush v. Wyeth*, 619 F.3d 632, 646 (6th Cir. 2010) (reversing district court finding preemption); *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85, 87-88 (2d Cir.

this Circuit have consistently rejected it. *See, e.g., Hill*, 944 F. Supp. 2d 943 (E.D. Cal. 2013)(claims defendant "should have altered the FDA-approved prescribing information" not preempted).

In *Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264 (W.D. Okla. 2011), the lone case cited in Defendants' motion which found impossibility, plaintiff alleged the Effexor label failed to adequately warn about the risk of suicide. While the FDA intensely studied the link between suicidality and SSRIs, it required all SSRIs to have identical warnings, and kept a tight rein on any language describing postmarketing reports. *Id.* at 1272. In 2002, Wyeth proposed an expanded warning relating to pediatric patients, but the FDA rejected it. *Id.* at 1276. In 2003 and 2004, Wyeth twice used the CBE to expand the warning, and the FDA twice directed them to remove it. *Id.* Thus, "the lengthy regulatory history" reflected the FDA's "reluctance to consider a warning which it believed might reduce the use of antidepressants and thereby undermine the benefits of their use in treating depression." *Id.* Yet, *Dobbs* was an outlier even among SSRI opinions.[17]

Defendants' motion relies heavily upon *Gaeta v. Perrigo Pharms. Co.*, 630 F.3d 1225 (9th Cir. 2011), which was vacated by 132 S. Ct. 497 then reversed by the Ninth Circuit, 469 Fed. Appx. 556, because it involved generic drugs.[18] *Gaeta* simply does not help Defendants. *Gaeta* rejected Defendants' argument that anything more than "passing

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2006) (pre-*Levine*, reversing district court finding preemption); *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 390 (7th Cir. 2010) (reversing district court finding preemption); *Lefaivre v. KV Pharm. Co.*, 636 F.3d 935, 938-39 (8th Cir. 2011) (reversing district court finding preemption). If Defendants are correct about the "ultimate inquiry" for preemption, then all of these cases were wrongly decided.

[17] "[T]he court is aware that other courts applying the *Levine* clear evidence standard in the context of SSRI label warnings have universally rejected the manufacturers' evidence as insufficient." *Dobbs*, 797 F. Supp. 2d. at 1277.

[18] *Gaeta* did not limit its "impossibility" analysis to the CBE regulations, but ***also*** held "nothing prevented Perrigo from seeking a prior approval from the FDA for a label change" and held Perrigo could have "suggest[ed] that the FDA send a 'Dear Doctor' letter to heath care professionals, warning them of the risks." 630 F.3d at 1235. Defendants make no effort to address either holding.

attention" by the FDA amounts to "clear evidence" the FDA would reject a warning. *Id.*[19] Instead, *Gaeta* carefully reviewed the entire regulatory history, recognized that the FDA "concluded that there was 'no need to propose a … warning at this time,'" and nonetheless held such decision by the FDA did ***not*** amount to "clear evidence" the FDA would have rejected the warning proposed by the plaintiffs.[20]

Apart from *Dobbs*, the lone district court case finding preemption in a branded prescription drug product liability case is *Glynn v. Merck Sharp & Dohme Corp. (In re Fosamax Prods. Liab. Litig.)*, 951 F. Supp. 2d 695 (D.N.J. 2013).[21] Post-trial,[22] the district court held that plaintiff's failure-to-warn claims were preempted because Merck had submitted a proposed labeling change and the FDA rejected it. *Id.* at 703. Notably, the rejection alone was not sufficient to prove preemption: the district court ***also*** held there was no "evidence that Defendant's PAS was rejected due to language," and no "evidence that Defendant could have submitted a CBE supplement to change the Precautions section," and no evidence "Defendant failed to provide all the information it had on femur fractures to the FDA and that Defendant failed to warn the FDA as soon as there was reasonable evidence of a causal association..." *Id.* at 704–05. Defendants here cannot establish ***any*** of the above, and they have vehemently objected to discovery into those issues, most particularly whether they provided such information.

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[19] "The [*Levine*] Court, however, did not clarify what would amount to 'clear evidence.' Rather, the only guidance this court has is that the evidence presented in *Levine* was insufficient to meet the clear evidence standard." *Gaeta*, 630 F.3d at 1235.

[20] *Gaeta's* rejoinder applies equally well to the Defendants here: Defendants "insistence that the FDA considered and rejected [the warnings at issue] is—just like in *Levine*—nothing more than creative paraphrasing of the FDA's regulations …" 630 F.3d at 1237.

[21] *Glynn* is the only post-*Levine* case in which any of the Defendants have prevailed on an impossibility preemption defense; presumably, Defendants elected not to cite it because it shows how high the bar is set and shows the need for a complete factual record.

[22] The Court in *Glynn* "reserved decision on the federal preemption motion until there was a complete trial record in the case." 951 F. Supp. 2d at 700. Such does little to bolster Defendants' pre-discovery demand that this Court give dispositive effect to their fact-intensive affirmative defense.

Indeed, even where the FDA actually does reject a relevant warning, such is generally ***still*** insufficient to prove the affirmative defense of preemption in light of the *Levine* requirement that a defendant ***also*** show the label rejection was "because the agency deemed such a warning inappropriate." *Wells ex rel. J.W.*, 2013 U.S. Dist. LEXIS 13191, 20–21 (W.D. Okla. Jan. 31, 2013).[23]

As shown above, the *sine qua non* of impossibility preemption is clear evidence that, as a factual matter, the manufacturer proposed a warning but the FDA either rejected it or "intended to prohibit it from strengthening the warning about [the drug] because the agency deemed such a warning inappropriate." *Levine,* 555 U.S. at 572. The FDA's inaction and rejection of citizen's petitions is insufficient, even where the FDA has been carefully following an issue for years. *See, e.g., Mason,* 596 F.3d at 395 ("Overall, we do not find the FDA's rejection of the citizen petitions or its call to do more research very compelling for either side."); *accord Forst v. Smithkline Beecham Corp.*, 639 F. Supp. 2d 948, 954 (E.D. Wis. 2009).[24]

Preemption of a branded prescription drug claim demands either (a) the FDA's express rejection of multiple proposed warnings and CBEs because the FDA felt such would be contrary to the public health (*Dobbs*) or (b) the FDA's rejection of a proposed warning coupled with no argument the FDA would have approved a modified label, no argument for a CBE, and no evidence the defendant concealed data from the FDA (*Glynn*). Here, Defendants do not even have the *initial* element — a proposed warning — must less clear evidence of the rejection or intent to reject. *See, e.g., In re Actos (Pioglitazone) Prods. Liab. Litig.*, 2014 U.S. Dist. LEXIS 1749 at *35 ("the defendants

[23] Such is consistent with *Levine*: as the Seventh Circuit noted in *Mason*, "[t]aking *Levine* as a whole, it is clear from the ample administrative record that the FDA strongly considered a similar warning to the one the plaintiff proposed and the Court still did not find preemption." *Mason*, 596 F.3d at 393.

[24] "GSK implies that because the FDA never required an enhanced warning in the past, despite exhaustive and repeated review of SSRI safety issues, that the agency concluded such warnings were unwarranted and inappropriate. However, the court does not deem GSK's evidence sufficient to establish 'impossibility preemption.'" *Forst*, 639 F. Supp. 2d at 954.

offer no evidence that a stronger warning was proposed by Takeda and rejected by the FDA.").

II. DEFENDANTS HAVE NOT MET THEIR BURDEN OF PROOF

After *Levine*, the Supreme Court reiterated that preemption may not hinge on whether a party can "prove the counterfactual conduct of the FDA and brand-name manufacturer" and "should not involve speculation" about the federal agency's potential response to a hypothetical situation. *Mensing*, 131 S. Ct. at 2580. As Eli Lilly and Amylin described *Mensing* in the JCCP, "state law juries should not engage in this kind of speculation about what the FDA *might* have done if the manufacturer had made a different submission." *See* Declaration of Michael K. Johnson (hereafter "Johnson Decl."), Ex. I, p. 4 (emphasis in original). Defendants' motion, however, is wholly premised on "speculation" about what might have happened assuming "counterfactual conduct of the FDA and brand-name manufacturer."

Defendants have adduced ***no facts*** indicating the FDA "intended to reject" any label relating to pancreatic cancer, much less facts showing, "beyond peradventure," the FDA intended to reject any warning relating to pancreatic cancer. The record includes no regulatory history, no label proposals or CBE changes, no FDA rejections or even *comments* on proposed labels, and no evidence the FDA would deem a pancreatic cancer warning inappropriate. Indeed, the scant facts related by the Defendants — who control virtually all of the relevant evidence — are shockingly inaccurate.

A. The FDA Has Not "Specifically Rejected" A Link To Pancreatic Cancer, But Has Instead "Not Reached A Final Conclusion"

Defendants brazenly assert the FDA "conducted a comprehensive evaluation of the scientific evidence concerning pancreatic cancer [and] FDA specifically rejected that claim,"[25] and then "published its assessment of incretin-based therapies and the risk of pancreatic cancer" in the NEJM. Defs' Br., pp. 1, 7, 8. This stretches the scope of the

[25] Defendants falsely attribute the "comprehensive evaluation" language to the FDA's March 14, 2013 Drug Safety Communication. The term "comprehensive" appears nowhere in that document.

review, which was on its face limited to "comprehensive evaluations *of a safety signal arising from postmarketing reports*," *i.e.*, the specific reports identified by the FDA in the NEJM article, rather than the entirety of the drugs' pancreatic safety. More disturbing, however, is the Defendants' shameless omission of the FDA's actual conclusion: "**The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship**." Such is plainly not the FDA "specifically rejecting" Plaintiffs' claims; it is the FDA continuing to investigate Plaintiffs' claims. The Citizen's Petition denial, in turn, includes a mere two paragraphs on pancreatic cancer, in which the FDA relates that the data it has been provided is "indeterminate" and that it "will continue to monitor and to review available safety information." Defs' Ex. B-38.

Even if the FDA *had* conducted a "comprehensive evaluation," and *had* expressly concluded there was no such link, such would *not* be sufficient to establish preemption, as shown by the SSRI cases recounted by *Dobbs*, none of which found preemption. Even in *Dobbs*, the FDA's close watch over SSRIs was not by itself enough: the Court found it "highly persuasive" that the FDA had ***also*** rejected the manufacturers' CBEs. *Dobbs*, 797 F.Supp.2d at 1276.

B. The FDA Has Not Independently Verified The Adequacy Of The Warnings Relating To Pancreatic Cancer

Defendants repeatedly assert that the FDA has independently "endorsed" the "adequacy" of their products' warnings relating to pancreatic cancer. Defs' Br., pp. 1, 2, 3, 9, 11, 18, 20. Even taking this assertion at face value does not support preemption; it is axiomatic that the FDA believes the labeling is adequate for *all* approved drugs, but "the mere fact that the FDA approved Phenergan's label does not establish that it would have prohibited such a change." *Levine*, 555 U.S. at 572.

Moreover, the quotation is so edited that it does not fairly represent the text from which it came.[26] Viewed in context, the language that "current knowledge is adequately

[26] "Although the totality of the data that have been reviewed provides reassurance, **pancreatitis** will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. The FDA and

reflected in the product information or labeling" relates ***solely to pancreatitis***. Indeed, what "further harmonization" could be done with regard to pancreatic cancer? The drugs in this MDL are all wholly silent on the subject, and thus wholly "harmonized" — but the drugs *do* have varying warnings relating to ***pancreatitis***.

C. The Labels Themselves Show The FDA Does Not Wait For Definitive Proof Before Allowing A Warning

Defendants claim the "FDA can only approve a warning as part of the labeling if there is 'reasonable evidence' of a causal association between the medication and a particular risk." Defs' Br., p. 4.[27] In reality, per *Levine* and the CBE, they may always unilaterally add warnings, but they are *required* to amend their label as soon as such an association appears; as the regulations state, "a causal relationship need not have been definitely established"[28] before that obligation attaches. Indeed, the labels in this very litigation reveal how specious Defendants' claim is. The NEJM article upon which Defendants' rely ***also*** concludes that "assertions concerning a causal association between incretin-based drugs ***and pancreatitis …*** are inconsistent with the current data," and yet ***all*** of the drugs in this MDL actually warn about pancreatitis. Victoza, for example, warns about pancreatitis in the Indications and Usage (1.1), the Warnings and Precautions (5.2), Adverse Reactions (6.2), Patient Counseling Information (17.4), and Medication Guide. Under Defendants' argument, the FDA would not and cannot approve such a warning, and thus Victoza is misbranded by the inclusion of that warning.

Indeed, the FDA's letter of March 25, 2014, shows how the FDA is more than willing to warn about serious risks *even where the FDA is still investigating a causal association*. The Citizen's Petition stated "the major safety issue with Victoza" related to "thyroid tumors" in rodent studies. Defs' Br. Ex. B-20. The FDA responded that "it is

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the EMA believe that the current knowledge is adequately reflected in the product information or labeling, and further harmonization among products is planned in Europe." Emphasis added. Full quote on page 3 of this brief.

[27] Defendants cite as support "21 C.F.R. § 201.57(e)," which does not exist.

[28] The real regulation is 21 C.F.R. § 201.57(c)(6). Per *Levine*, this misbranding regulation is not "a floor and a ceiling for drug regulation," and state tort law may demand more.

unknown whether there is an association between Victoza treatment and thyroid C-cell tumors in humans," *id.* at Ex. B-23, but **Victoza's label *repeatedly* warns about thyroid C-cell tumors**. Thyroid C-cell tumors are addressed in Warnings and Precautions (5.1), Nonclincal Toxicity (13.1), Patient Counseling Information (17), and the Medication Guide, in which **"What is the most important information I should know about Victoza?"** is answered **"1. Possible thyroid tumors, including cancer."** *See* Johnson Decl., Ex. M-N. Indeed, the Black Box is the only warning that is *not* amenable to the CBE, but instead requires FDA approval, and the FDA approved a Black Box warning for thyroid C-cell tumors *despite its belief that the causal relation is "unknown."*

It is not hard to see why the FDA would permit a warning about tumors, neoplasms, or cancers, even if the FDA still believed the data was "unknown" or "indeterminate." Cancer is 'the emperor of all maladies,' the cause of one out of every four American deaths. No information could be more pertinent to a physician prescribing a medication, or a patient taking one, than the possibility that the medication might contribute towards the development of cancer.

D. There Is Ample Evidence Of An Association Between Defendants' Drugs And Pancreatic Cancer

Defendants offered no experts to shepherd into evidence their extensive assertions about scientific evidence, and thus those assertions are inadmissible and cannot be used to sustain their burden of proof. Further discussion is hardly warranted, but, to avoid any appearance of waiver, Plaintiffs reiterate that they have properly plead, based upon sound peer-reviewed science, multiple mechanisms by which Defendants' drugs may have the capacity to cause cancer as well as the existence of empirical epidemiological evidence confirming this relationship. Plaintiffs' Master Complaint describes in detail how incretin mimetic use contributes to pancreatic inflammation, increased cell turnover, and reduced immune system surveillance, *Complaint* at ¶¶45–63, all of which contribute to the initiation and progression of pancreatic cancer.[29] Plaintiffs' Master Complaint also

[29] *See, e.g.*, Ilya Gukovsky et al, Inflammation, Autophagy, and Obesity: Common Features in the Pathogenesis of Pancreatitis and Pancreatic Cancer, Gastroenterology Vol.

describes how incretin mimetic use accelerates the progression of pancreatic intraepithelial neoplasia (PanIN), thereby turning premalignant lesions into malignant cancers, *Complaint* at ¶¶72–74.

But Plaintiffs' Complaint did not need to be, and was not intended to be, a definitive statement of the state of the science, and there is sound peer-reviewed science supporting other causal mechanisms as well. Pancreatic stellate cells ("PSCs") increase inflammation, activate STAT3, and produce galectin-1, all of which are widely accepted as contributing towards the initiation and progression of pancreatic cancer.[30] Incretin mimetics have been shown to "induce[] cell proliferation of activated PSCs without increasing release of inflammatory mediators," which suggests "chronic treatment with GLP-1R agonists could lead to proliferation/chronic activation of PSCs…"[31] This relationship *alone* could show incretin mimetics to be a substantial causative factor,[32] and it is just one of many mechanisms being pursued by researchers, which is presumably why the FDA has "not reached a final conclusion."[33]

All of the above was found by researchers with access to only a tiny fraction of the scientific data available on incretin mimetics; the great weight of scientific data lies with the Defendants' under lock and key, and they have shown every intention of doing their utmost to keep it there.

144, Issue 6, pp. 1199–1209, 1202 (May 2013), describing how "chronic inflammation" of the pancreas caused by, *inter alia*, "environmental factors" can "contribute to [pancreatic cancer] initiation and progression." *See* Johnson Decl., Ex. J.

[30] Minote V. Apte et al, A Starring Role for Stellate Cells in the Pancreatic Cancer Microenvironment, Gastroenterology Vol. 144, Issue 6, pp. 1210-1219 (May 2013). *See* Johnson Decl., Ex. K.

[31] Nakamura T. et al, PSCs and GLP-1R: occurrence in normal pancreas, acute/chronic pancreatitis and effect of their activation by a GLP-1R agonist, Laboratory Investigation (2014) Vol. 94, 63-78. *See* Johnson Decl., Ex. L.

[32] An expert witness need not identify the sole cause of a medical condition. "It is enough that [the] condition be a substantial causative factor." *Messick v. Novartis Pharms. Corp.*, 2014 U.S. App. LEXIS 6257 at *13 (9th Cir. Cal. Apr. 4, 2014).

[33] *See, e.g.*, Prof. Fred Gorelick, "GLP-1 based therapies and pancreatic disease: review of potential mechanisms," presented at the EASD Barcelona 2013 Conference, *available at* http://www.easdvirtualmeeting.org/resources/6257.

III. IF THIS MOTION IS NOT DENIED OUTRIGHT, PLAINTIFFS SHOULD BE ALLOWED MEANINGFUL DISCOVERY ON ALL PREEMPTION ISSUES BEFORE THE MOTION IS HEARD

Impossibility preemption is a demanding, fact specific defense. Defendants moved for summary judgment before responding to Plaintiffs' general causation discovery, and discovery is currently stayed as to regulatory, labeling, and related areas pertinent to the affirmative defense of preemption.[34] Yet even the limited discovery done so far has revealed evidence suggesting that additional discovery would provide further grounds for the denial of this motion. If the motion is not denied outright, it should be continued indefinitely so Plaintiffs may take full discovery on the issues presented, as provided by Fed. R. Civ. P. 56(d).[35]

A. Impossibility Preemption Analysis Is Highly Fact Intensive

To satisfy the "demanding" standard established by *Levine*, a court must review a drug's regulatory history, labeling history (including all proposals, FDA responses, and CBEs), and the manufacturer's communications with the FDA. "[A]pplication of the clear evidence standard is ***necessarily fact specific***." *Dobbs*, 797 F. Supp. 2d at 1270 (emphasis added); *see also Mason*, 596 F.3d at 396 (7th Cir. 2010) (in-depth factual analysis required "in light of the ***extensive showing*** required by *Levine[.]*") (emphasis added). Since the preemption inquiry is fact-specific and Defendants have not disclosed the facts, Plaintiffs request the opportunity for meaningful discovery to develop a proper factual record before this motion is heard, as contemplated by Rule 56(d).

B. Plaintiffs Have Not Been Allowed Meaningful Discovery To Develop The Facts On Preemption Issues

Discovery has been limited to general causation only, per Dkt. No. 325. Plaintiffs have not begun, much less completed, discovery of issues that bear upon the FDA's

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[34] Defendants have "create[d] a procedural quagmire in which the Plaintiffs and the Court are stuck addressing repeated Rule 56(d) responses to delay consideration of the Defendants' motions, because discovery would still be ongoing." Dkt. No. 309, p. 8.

[35] Plaintiffs met and conferred with Defendants in an effort to have the motion withdrawn without prejudice to a later re-filing after discovery was complete, but Defendants wanted the motion heard on the current record. Johnson Decl., ¶¶ 15-16 and Ex. C-D.

"intent" to accept or reject any proposed warnings. Defendants seek to meet their burden by asking this Court to speculate about what the FDA *might* do in response to a hypothetical warning, but the full regulatory history would show what the FDA *actually has done* in response to proposed warnings, and would shed light on the FDA's true "intent" with regard to pancreatic cancer. The FDA approved Victoza bearing a variety of thyroid tumor and cancer warnings, including a Black Box, despite the FDA's own belief that the causal association is "unknown." Discovery would reveal how the FDA has reacted to Defendants' proposals for pancreatic cancer warnings, if any.

Even under Defendants' own erroneous interpretation of *Levine*, to prevail, they must prove what the FDA "would have" done in response to hypothetical pancreatic cancer warnings. Yet, as Defendants themselves contend, in such a hypothetical submission, the Defendants would have to provide to the FDA the evidence supporting such a causal relationship. This means that for this Court to assess Defendants' preemption defense, it must *also* assess all of the scientific evidence in Defendants' possession relating to pancreatic cancer, including all studies and all adverse events. *See, e.g.*, *Glynn* at 704–05 (including in preemption analysis whether "Defendant failed to provide all the information it had on femur fractures to the FDA and that Defendant failed to warn the FDA as soon as there was reasonable evidence of a causal association between Fosamax and [femur fractures].").[36]

Discovery of the data in Defendants' possession and the identification of the data withheld from the FDA would similarly enable the Court and the Plaintiffs to evaluate

[36] Defendants may contend that any such discovery is preempted by *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001). *Buckman* held that plaintiffs do not have standalone "fraud-on-the-FDA" claims. *Buckman* has no bearing on the scope of discovery necessary to evaluate a manufacturer's affirmative defense. *See, e.g., Glynn II* (*In re Fosamax)*, 2014 U.S. Dist. LEXIS 42253 at *58 (D.N.J. Mar. 26, 2014) (in case where FDA rejected warning, the court allowed plaintiffs discovery and trial "to show that providing such information to the FDA would have changed the FDA's conclusion that a Precaution was not warranted," then finding preemption because plaintiffs had not made such a factual showing); *In re Yasmin and YAZ*, 2011 WL 6302287 at *11 (S.D. Ill. Dec. 16, 2011) ("*Buckman* is a claim preemption case focusing on fraud-on-the-FDA claims, not an evidence preclusion case.")

whether the FDA's "intent" is merely the product of Defendants' selective production of information. Even the limited discovery available has shown that Eli Lilly and Amylin, for example, have for years based their reports to the FDA on a statistical analysis they believe is "not well-suited to this task," which they "knew going in," but there is no indication they ever shared that belief with the FDA.[37]

C. The Legal Standards For Allowing Discovery Under Fed. R. Civ. P. 56(d)

Rule 56(d) provides time for litigants to engaging in meaningful discovery and develop evidence to avoid (or, here, to defeat) summary judgment when they have not yet had the chance to do so. *Burlington Northern Santa Fe R. Co. v. Assiniboine and Sioux Tribes of Fort Peck Reservation*, 323 F.3d 767, 773 (9th Cir. 2003) (discussing Rule 56(f), the predecessor to the current Rule 56(d)). "The general principle of Rule 56(f) is that 'summary judgment should be refused where the nonmoving party has not had the opportunity to discover information that is essential to his opposition.'" *Provide Commerce, Inc. v. Hartford Fire Ins. Co.*, 2014 WL 1155311 at *2 (S.D. Cal. March 21, 2014), quoting *Price v. Western Resources, Inc.*, 232 F.3d 779, 783 (10th Cir. 2000) (quoting *Anderson v. Liberty Lobby*, 477 U.S. 242, 250 n. 5 (1986)).

Courts have discretion to either deny or continue a motion for summary judgment if the party opposing the motion "shows by affidavit or declaration that, for specified reasons, it cannot present facts essential to justify its opposition." Fed. R. Civ. P. 56(d). Plaintiffs have submitted the required declarations (see Part III(D) *infra*). This Court may therefore continue Defendants' preemption motion to allow Plaintiffs "to discover essential facts." *Cal. Union. Ins. Co. v. American Diversified Sav. Bank*, 914 F.2d 1271, 1278 (9th Cir. 1990), *cert. denied*, 498 U.S. 1088 (1991).

[37] *See* Declaration of Neal L. Moskow ("Moskow Decl."), ¶¶ 9-20 and Ex. G-R thereto, including LILLY01427987 (internal email in October 2009 regarding i3 Aperio database); compare BY00412482 (November 2009 transmittal letter to FDA referencing results of Aperio); AMLYN02730943 (March 2011 transmittal letter to FDA referencing results of Aperio).

A lengthy continuance to allow discovery is appropriate when the plaintiff in a complex pharmaceutical product liability case is confronted with an early motion for summary judgment based on impossibility preemption. The need for extensive discovery is **"due to the fact-intensive nature of the preemption inquiry."** *Estate of Cassel v. Alza Corp. and Janssen Pharmaceuticals, Inc.*, 2014 WL 856023 at *1 (W.D. Wis. Mar. 5, 2014) (emphasis added). In *Estate of Cassel*, plaintiffs' decedent died from an alleged fentanyl overdose. The court granted plaintiffs' request for a six-month stay to complete discovery regarding the defendants' transdermal fentanyl patch. *See Estate of Cassel v. Alza Corp. and Janssen Pharmaceuticals, Inc.*,, No. 3:12-cv-00771-wmc, Order (W.D. Wis. May 3, 2013) (unpublished), Johnson Decl. Ex. E.

D. Plaintiffs Have Shown That Additional Discovery On Preemption Issues Would Preclude Summary Judgment

A party seeking discovery under Rule 56(d) "must identify . . . the specific facts that further discovery would reveal, and explain why those facts would preclude summary judgment." *Provide*, 2014 WL 1155331 at *2, citing *California v. Campbell*, 138 F.3d 772, 779 (9th Cir.1998). There are already ample grounds on which to deny this motion, but Plaintiffs have submitted declarations detailing how additional discovery can be expected to further demonstrate that Defendants have not met their burden of proof on impossibility preemption.

1. Declaration of Michael K. Johnson

The Johnson Declaration attaches representative copies of the general causation discovery served on Defendants.[38] In conjunction with this motion response, the Johnson Declaration also explains why Defendants' responses can be expected to provide additional grounds for denial of the preemption motion.

[38] Defendants' responses to Plaintiffs' general causation discovery were due May 8, 2014. Two Defendants served responses that evening. The other two asked for and received an extension to May 9. This motion response was due May 12, the next business day after May 9. These timing constraints precluded Plaintiffs from addressing specifics from Defendants' discovery in this response. *See* Johnson Decl., ¶¶ 11-12 and Ex. A-B.

Plaintiffs' discovery sought disclosure of the data in Defendants' possession regarding the relationship between incretin medications and pancreatic cancer. Plaintiffs also sought disclosure of the information Defendants provided to and withheld from the FDA on that subject. Further information was sought regarding all requests for pancreatic cancer warnings or label changes submitted by Defendants to the FDA, and the FDA's responses to such requests. All of this information can reasonably be expected to bear on Defendants' preemption motion because it will show whether the FDA has been fully informed of the connection between incretin drugs and pancreatic cancer, and will show how the FDA has actually – as opposed to hypothetically – addressed those issues. *See*, *e.g.*, Johnson Decl., ¶¶ 19-29 and Ex. A-B.

2. Declaration of John M. Restaino

The Restaino Declaration focuses on "missing" reports of known incidents of pancreatic cancer occurring in connection with Byetta clinical trials. The declaration describes in detail three incidents of pancreatic cancer discovered during review of documents produced by Defendants Amylin and Eli Lilly.[39] Based on the information available to date, it appears that these incidents were either not reported to the FDA at all, reported incorrectly as not being associated with the clinical trial in which the cancer victim had been enrolled, or reported incorrectly as not being causally related to the use of Byetta when causation had yet to be determined. The additional discovery needed to confirm and explain these "missing" pancreatic cancers is also outlined.[40] *See* Restaino Decl., ¶¶ 5-19.

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[39] In general, more documentation has been available regarding Byetta than the other incretin drugs because only Byetta was involved in the JCCP proceedings before Judge Highberger regarding pancreatitis. *See* Restaino Decl., ¶ 20.

[40] Data "missing" from clinical trials is a growing problem. An FDA investigator quoted late last year in an article published in the British Medical Journal noted that "one can hide a multitude of sins in missing data." The investigator described the clinical trial system as "broken," but said proposed reforms were unlikely to be adopted: "the drug companies will resist tremendously because right now, 100% true, they control the data. [It's] very, very difficult to verify whether data are complete or accurate." *See* Johnson Decl., Ex. F.

Pancreatic cancer is a relatively rare event. No pancreatic cancers were reported as associated with the Byetta clinical trials through September 2009, and only one through September 2010. The addition of several more incidents of associated pancreatic cancer would be statistically significant and could, in and of itself, provide the basis for a warning about the risks of pancreatic cancer associated with the use of incretin medications.[41] Restaino Decl., ¶ 21. Plaintiffs have no reason to believe the FDA is even aware of the under-reporting suggested by Defendants' data.

3. Declaration of Neal L. Moskow

The Moskow Declaration also addresses specific fact issues raised in documents produced by Defendants Amylin and Lilly. Those issues include the existence of pancreatic cancer safety signals, the failure to perform causality assessments for reported pancreatic cancers, and the use of statistical analyses known by Defendants to be underpowered, not robust, not well suited to the task for which they were used, and not capable of addressing incidence rates for pancreatic cancer. Additional discovery needed to fully understand and explain all of the above issues is also outlined in the Moskow Declaration. *See* Moskow Decl., ¶¶ 4-20, 24.

The information addressed in the Moskow Declaration may, in and of itself, be sufficient to have warranted warnings about the risks of pancreatic cancer as of 2008 or 2009. Moreover, based on the companies' internal documents, it is apparent that Defendants were providing the FDA with statistical analyses of pancreatic cancer

[41] Plaintiffs have significant concerns about the as-yet-unknown number of other pancreatic cancers that arose in the course of the incretin clinical trials. Experience suggests that if one pancreatic cancer victim from a clinical trial was not reported, or not properly reported as a "clinical trial" serious adverse event, the same was done with others. Given the coding practices apparently followed, if pancreatic cancer symptoms forced a participant to withdraw from a clinical trial, but the participant was not formally *diagnosed* with pancreatic cancer until more than 30 days later, the participant was not considered an adverse event or serious adverse event *within that clinical trial*, and was therefore not reported as such to the FDA (or EMA). Locating and correcting reporting errors, whether accidental or intentional, is a painstaking and time-consuming process that requires a thorough review of each reported instance of pancreatic cancer, whether it is initially tied to a clinical trial or not. *See* Restaino Decl., ¶¶ 10, 15, 21-22.

incidence rates that Defendants knew to be inadequate. *See* Moskow Decl. ¶¶ 21-22. How the FDA would have responded had it been provided with complete and accurate information remains unknown.

4. Other Discovery and its Effect on Preemption

The minimal discovery obtained so far already indicates that Defendants have negligently or intentionally withheld material information from the FDA, or falsified, misrepresented or otherwise conveyed erroneous material information to the FDA regarding the causal relationship between incretin medications and pancreatic cancer. *See generally* Restaino Decl.; Moskow Decl. If further discovery confirms and expands on Defendants' withholding of material information, then Defendants cannot possibly prove the FDA intended to *reject* a label change regarding pancreatic cancer based on *correct and complete* information.

Other specific types of discovery requests that can be expected to raise genuine issues of material fact to defeat preemption include the following:

a. Preclinical, Nonclinical and Human Studies

Plaintiffs still do not know if any of Defendants' studies were biased by selection techniques (*e.g.*, using animal models known from the outset to be unlikely to show pancreatic damage, or "screening out" potential clinical trial participants with known risk factors for pancreatic cancer). Similarly, Plaintiffs have yet to learn how much of the raw data, histology, specimens, etc., were provided to the FDA for key studies undertaken by Defendants. This information is directly relevant to an impossibility preemption analysis, and Plaintiffs should have the opportunity to obtain and review that information before responding to this motion. *See* Johnson Decl., ¶ 21.

b. Observational and Epidemiological Studies

Plaintiffs do not know if Defendants have undertaken observational and/or epidemiological studies reported or not reported to the FDA. Questions on this topic are part of Plaintiffs' general causation discovery. The results of any such studies may directly impact the need for warnings. All questions relating to such studies should be fully answered before any preemption motion is addressed. *See* Johnson Decl., ¶ 23.

c. Studies Undertaken to Determine Causal Connections

Plaintiffs also do not know if Defendants have undertaken studies specifically to determine whether there is a causal connection between the incretin medications and pancreatic cancer, and whether the results of any such studies were reported or not reported to the FDA. Questions on that subject are again part of Plaintiffs' general causation discovery. Such questions directly bear on warnings, and they should be fully answered before any preemption motion is heard. *See* Johnson Decl., ¶ 24.

d. Adverse Events

Plaintiffs are entitled to Defendants' worldwide post-marketing adverse event reports, data, source documents, internal individual and aggregate analyses and evaluations, and causality assessments for pancreatitis and pancreatic cancer with respect to their respective incretin medications. It is well understood that adverse event reports "can be effective in revealing unusual or rare adverse events that occur with the use of medications, *and such reports may often be sufficient to assign causality*." Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs, JAMA, 281:9 (March 3, 1999) (emphasis added), Johnson Decl., Ex. G. Plaintiffs have also learned that at least one of the Defendants here – Merck – uses its post-marketing adverse event reports "in aggregate" for exactly the purpose described in the scientific literature: to make *causality assessments* between its products, such as Januvia and Janumet, and adverse events such as pancreatic cancer. *See* Johnson Decl., Ex. H, Dep. Tr. of Linda Hostelley, Merck Vice President of Global Safety, at 60:22-63:17.

The adverse event reports, databases, source documents, internal analyses and evaluations, and causality assessments were requested in Plaintiffs' general causation discovery. A full and complete response is required before any preemption motion can be meaningfully addressed. Errors in adverse event reporting can have a direct effect on whether warnings about the adverse event in question should be issued. Johnson Decl., ¶¶ 25-26.

e. Communications with the FDA

Plaintiffs do not know what information in Defendants' possession regarding pancreatic cancer has and has not been communicated to the FDA. That information was requested in Plaintiffs' general causation discovery, and it is clearly relevant to a preemption analysis. *See* §§ I-II, *supra*.

The Defendants' communications with the FDA on the very subject on which they now seek preemption should not be a mystery. Plaintiffs ask the Court to note that Defendants have not even *alleged* in this motion – much less proven – that they have cooperated with the FDA, or that they have provided the FDA with all of their material information regarding the causal link between incretin medications and pancreatic cancer. If material information on that causal link has been withheld, there is no reason to believe that appropriate warnings will not be allowed by the FDA once the correct information is provided. Again, Plaintiffs cannot properly address this preemption motion until they have the basic information about what Defendants have provided to and withheld from the FDA. *See* Johnson Decl., ¶ 21, 29.

The FDA's communications with Defendants are also conspicuously absent from this motion. Nowhere is it shown that the FDA has told any Defendant that the FDA even believes – much less knows – that it has been provided with truthful, accurate and complete information regarding incretins and pancreatic cancer. The record is also silent on whether the FDA has asked any or all Defendants to submit proposed warnings on the link between incretins and pancreatic cancer. This again is basic information that Plaintiffs have requested in discovery, but have yet to receive. It is premature to address this impossibility preemption motion when so little information has been provided about Defendants' communications with the FDA on the subject of warnings for pancreatic cancer. *See* Johnson Decl., ¶ 29.

The above examples illustrate why an impossibility preemption motion is highly inappropriate before discovery has been completed. On the current record, it is entirely possible that the FDA is preparing to approve a proposed warning for pancreatic cancer *tomorrow*. Neither Plaintiffs nor the Court can know the status of such matters pending

before the FDA. Only Defendants have a basis to know, and they have chosen not to share that information. Until discovery is complete, and Defendants are forced to disclose the information necessary for preemption analysis, Plaintiffs should not have to respond to this motion.

E. Defendants Cannot Have It Both Ways

Defendants specifically requested that the Court foreclose discovery on *all matters other than general causation* until ruling on *Daubert* motions. The Court granted that request. Defendants have now changed course, filing a very fact-intensive motion that Plaintiffs cannot properly respond to without broad-based discovery on issues that extend beyond general causation, including all regulatory matters and FDA communications that bear on each Defendant's incretin medication(s). Since Defendants have set aside their "straight ahead to *Daubert*" plan, the discovery restrictions tailored to that plan should also be set aside. Plaintiffs need both additional time for discovery and an expanded scope to engage in discovery of all the issues raised by Defendants' affirmative defense.

CONCLUSION

Plaintiffs respectfully request that Defendants' preemption motion be denied; and if not denied, be continued or taken off the calendar until Plaintiffs have had the opportunity to take the discovery necessary to fully address the motion. That discovery includes the general causation interrogatories and document requests previously ordered by the Court; the custodial file productions previously ordered; and full discovery on the regulatory history of Defendants' products, their communications with the FDA, and the related matters invariably called into play when a defendant attempts to prove up a preemption defense.

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PLAINTIFFS' COUNSEL

s/Michael K. Johnson
Michael K. Johnson
Kenneth W. Pearson
JOHNSON BECKER, PLLC
33 South Sixth Street, Suite 4530
Minneapolis, Minnesota 55402

Telephone: (612) 436-1800
Facsimile: (612) 436-1801
mjohnson@johnsonbecker.com

Ryan L. Thompson
WATTS GUERRA LLP
5250 Prue Road, Suite 525
San Antonio, Texas 78240
Telephone: (210) 448-0500
Facsimile: (210) 448-0501
rthompson@wattsguerra.com

Hunter J. Shkolnik
NAPOLI, BERN, RIPKA & SHKOLNIK LLP
350 Fifth Avenue
New York, New York 10018
Telephone: (212)267-3700
Facsimile: (212)587-0031
hunter@napolibern.com

Tor A. Hoerman
Kenneth J. Brennan
TORHOERMAN LAW LLC
101 W. Vandalia Street, Suite 350
Edwardsville, Illinois 62025
Phone: (618) 656-4400
Facsimile: (618) 656-4401
thoerman@torhoermanlaw.com

Max Kennerly
THE BEASLEY FIRM
1125 Walnut Street
Philadelphia, PA 19107
Telephone: (215) 931-2634
Facsimile: (215) 592-8360
max.kennerly@beasleyfirm.com